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Albion Laboratories, INC.

P.O. BOX 750 • 101 NORTH MAIN STREET, CLEARFIELD, UTAH 84015 USA
PHONE: 801-773-4631 • TOLL FREE 800-453-2406 • FAX 801-773-4633

April 20, 1999

Office of Premarket Approval (HFS–200)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street S.W.
Washington DC 20204

VIA COURIER

RE: Notice of GRAS Determination for Ferrochel™, a Ferrous Bisglycinate Chelate

Dear Sir or Madam:

Accompanying this letter please find three originals of the Notice to U.S. Food & Drug Administration of "GRAS" Determination for Ferrochel™, a Ferrous Bisglycinate Chelate (the *"Notice"*) which is submitted by Albion Laboratories Inc. pursuant to the proposed FDA regulation, 21 CFR §170.36 (62 Fed. Reg. 18,960 April 17, 1997). Thank you in advance for your consideration of this Notice. Should you have any questions, please contact me.

Sincerely,

James C. Hyde
Vice President & General Counsel
ALBION LABORATORIES INC.

enclosures

cc: H. DeWayne Ashmead
Evan E. Jones, Jr.
Charles R. Whiting

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NOTICE TO U.S. FOOD & DRUG ADMINISTRATION OF "GRAS" DETERMINATION FOR FERROCHEL™, A FERROUS BISGLYCINATE CHELATE

Pursuant to Proposed Regulation
21 CFR §170.36,
62 Fed. Reg. 18,960 (April 17, 1997)

SUBMITTED BY:

ALBION LABORATORIES INC.
101 North Main
Clearfield, Utah 84015-2243
Ph. (801) 773-4631 • Fax (801) 773-4633
Toll Free (800) 453-2406

April 20, 1999

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[redacted]

NOTICE TO U.S. FOOD & DRUG ADMINISTRATION OF "GRAS" DETERMINATION FOR FERROCHEL™, A FERROUS BISGLYCINATE CHELATE

Pursuant to Proposed Regulation 21 CFR §170.36,
62 Fed. Reg. 18,960 (April 17, 1997)

I. INTRODUCTION

Albion Laboratories Inc. (the *"Company"*) submits this Notice (the *"Notice"*) to the U.S. Food and Drug Administration (*"FDA"*) pursuant to the proposed FDA regulation 21 CFR §170.36 (62 Fed. Reg. No. 74, pg. 18,690) (the *"Regulation"*), and relating to the Company's determination that its compound, a ferrous bisglycinate chelate with the trade name of *"Ferrochel™[1],"* is generally recognized as safe (*"GRAS"*) for the uses and purposes set forth and described herein. The substance which is the subject of this Notice is referred to hereinafter as *"Ferrochel."*

As a general description, Ferrochel is a free-flowing, fine powder consisting of ferrous iron which, through a chemical reaction based on patented processes, is bonded by coordinate covalent bonds to an amino acid (glycine) to form a molecule in which the iron atom is the closing member of two heterocyclic rings. This chemical bonding process is called "chelation" and the resultant molecule is generically called a "chelate."

The remainder of the following materials and information follow the outline of requirements of the Regulation.

II. EXEMPTION CLAIM; §170.36(c)(1)

As required by 21 CFR §170.36(c)(1), the following information and data are submitted by the Company, which claims that Ferrochel is GRAS for the uses and purposes described herein and is therefore exempt from the premarket approval requirements of the Federal Food, Drug, and Cosmetic Act (the *"Act"*).

A. Name and Address of Notifier.

Albion Laboratories Inc.
101 North Main Street
Clearfield, Utah 84015-2243
Phone: (801) 773-4631
Fax: (801) 773-4633

[1] *"Ferrochel"* is a proprietary trademark of the Company.

B. Common Name of Ferrochel.

Ferrous bisglycinate chelate. (For detailed information about the identity and specifications of Ferrochel, see Section *III* below).

C. Conditions of Use.

By providing this Notice the Company intends for Ferrochel to be used as a source of dietary iron for the food enrichment and fortification purposes that are presently authorized and permitted by applicable law or regulation in the United States.

D. Basis for the GRAS Determination.

The basis for the Company's determination of Ferrochel as GRAS is through scientific procedures. For a detailed discussion of the studies, data, materials and information that form this basis, see Section *V* below.

E. Availability of Data.

All of the data and information referenced herein or relied upon by the Company for its determination that Ferrochel is GRAS for the uses and purposes set forth herein are available to FDA for review or copying or will be sent to FDA upon request.

III. DETAILED INFORMATION ABOUT THE IDENTITY OF FERROCHEL; §170.36(c)(2)

As required by 21 CFR §170.36(c)(2), the Company provides the following information and data with respect to Ferrochel for purposes of its identification and specification.

A. Common Name: ferrous bisglycinate chelate

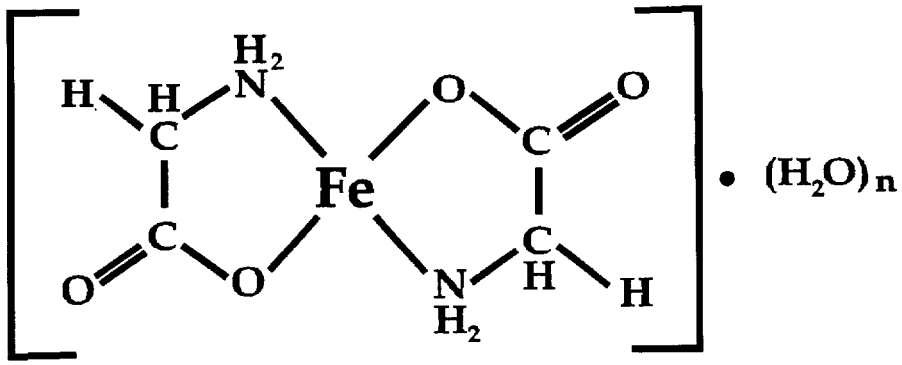
B. Trade Name: Ferrochel

C. Chemical Name: ferrous bisglycinate chelate

D. C.A.S. Registry Number: CAS-20150-34-9

E. Empirical Formula: $Fe(COOCH_2NH_2)_2$

F. Structural Formula: The structural formula of Ferrochel is shown below as elucidated by Fourier transformed mid-infrared spectroscopy and based on prior research of the Company's iron amino acid chelates utilizing electron paramagnetic resonance and mid-infrared spectroscopy:



G. Quantitative Compositions: Ferrochel has the following composition by weight: Fe 27% and chelated glycine 73%. The final commercial product that is sold and made available for the intended uses has the following typical composition.

Table No. 1
Typical Composition of Commercially Prepared Ferrochel

Component	Percent by Weight
Iron Bisglycinate Chelate	77.0%
Citric acid[2]	17.0%
Silicon dioxide[3]	< .01%
Maltodextrin[4]	2.0%
Moisture	4.0%
Total	100%

[2] Citric Acid is a GRAS substance pursuant to 21 CFR §184.1033.

[3] Silicon dioxide is an approved food additive as an anti-caking agent pursuant to 21 CFR §172.480, which is the purpose for its use in the manufacturing of Ferrochel.

[4] Maltodextrin is a GRAS substance pursuant to 21 CFR §184.1444.

H. Specifications For Ferrochel: Ferrochel meets the following specifications before release for commercial use.

Table No. 2
Commercial Specifications of Ferrochel

PROPERTY/METHOD	VALUE
Iron (elemental by inductively coupled plasma)	Not less than 20%
Color	Khaki Gray
Texture	Fine, light powder
Density (gravimetric)	0.500 - 0.750 g/cc
Particle size (standard screens)	100% through 80 mesh
Loss on ignition (8 h at 650°C)	70 - 72%
Total nitrogen (dry basis by elemental analysis)	10 - 12%
Solubility (25°C at product pH)	1 g/2.5 ml distilled H_2O
Moisture (1 h at 110°C)	Not greater than 7%
pH (1.0% in distilled H_2O, 25°C)	7.5 - 8.5
Heavy Metals Content:	Pb < 0.5 ppm Cd < 0.1 ppm Hg < 0.1 ppm As < 0.1 ppm Se < 0.1 ppm

I. Method of Manufacture: Ferrochel is manufactured under patented processes. Generally, ferrous iron is reacted with glycine in an aqueous environment under exacting reaction conditions to form the chelated compound. The other constituents of the commercial product are incorporated under specified manufacturing conditions. The solution is then dried to recover a powder by removing the water through spray drying or other effective drying methods. The physical properties and specifications of Ferrochel are verified under standardized quality control assays in accordance with applicable good laboratories practices as

guidelines and utilizing applicable AOAC methods. All ingredients used in the manufacture of Ferrochel are USP or food grade quality. In addition, all other ingredients used in the manufacture of the final commercial product are food grade or better.

IV. SELF-LIMITING LEVELS OF USE; §170.36(c)(3)

Issues regarding self-limiting levels of use of Ferrochel are addressed by (i) the applicable laws or regulations which currently permit and specify the level of iron enrichment in certain foods, (ii) the guidance regarding iron levels provided under the Recommended Daily Allowances (*"RDA"*) established by the Food and Nutrition board of the National academy of Sciences, and (iii) Current Good Manufacturing Practices (*"CGMP"*) that are applicable to and govern food manufacturers.

The RDAs have provided clear guidance on the amount of essential nutrients needed to sustain normal health. Further, CGMPs clearly state that ingredients added to foods should not exceed the amount reasonably required to achieve the intended purpose (21 CFR §182.1(b)(1)). These two guidelines have provided excellent guidance to manufacturers and distributors of iron fortified foods over many years.

Given these guidelines (RDA and CGMP) and the iron enrichment levels specified by applicable law or regulation for the fortification of foods, there is an essential and fundamental assurance in place that fortification with iron is, in principle, self-limiting. Hence, in view of these well established protections of public health and the exceptionally high NOAEL of Ferrochel (>500mg/kgbw/day; see attached Expert Panel Report), concerns of additional self-limiting levels of use of Ferrochel are not relevant to this Notice.

V. DETAILED SUMMARY OF BASIS FOR DETERMINATION; §170.36(c)(4)(i)

In connection with the Company's self-affirmation of Ferrochel as GRAS, the expert panel, which was retained to review the applicable and relevant data (the *"Expert Panel"*), prepared a written statement (the *"Expert Panel Statement"*) which provides a critical review of the data upon which the determination of Ferrochel as GRAS was made. The Expert Panel Statement is attached hereto at Exhibit A and is incorporated here by reference. The Expert Panel Statement is submitted in compliance with the requirements of §170.36(c)(4)(i). Two studies were specifically mentioned and relied upon by the Expert Panel in reaching its determination that Ferrochel is GRAS for the specified uses. Those studies are (i) the subchronic study in rats referenced at the last paragraph on page 1of the Expert Panel Report, and (ii) the nutritional study in young children referenced at the second paragraph on page 2 of the Expert Panel Statement where one liter of milk was fortified with 3 mg of iron as Ferrochel. Though not provided in the Expert Panel Statement, the specific published papers in which these studies are reviewed have the following citations:

=> Moved July to August 1999 Vol 37, No 7 P723-731

- Borzelleca JF, Jeppsen RB, *Safety Evaluation of Ferrous Bisglycinate Chelate*, Food and Chemical Toxicology, In Press (scheduled for publication July 1999, Vol. 37, No. 7). The complete subchronic study referenced in this paper is cited below as the study performed by Huntingdon Life Sciences in July 1997.

- Iost C, Name JJ, Jeppsen RB, Ashmead HD, *Repleting Hemoglobin in Iron Deficiency Anemia in Young Children through Liquid Milk Fortification with Bioavailable Iron Amino Acid Chelate*, Journal of the American College of Nutrition, Vol. 17, No. 2, pg. 187 (1998).

Additionally, set forth below is the list of other papers and studies that were evaluated and relied on by the Expert Panel in reaching its determination that Ferrochel is GRAS:

- *A Subchronic (3 Month) Toxicity Study of Ferrochel in the Rat Administered Via Diet*, Study No. 96-2503, Huntingdon Life Sciences, July 10, 1997.

- *Acute Oral Toxicity Study in the Sprague Dawley Rat (LD 50); Ferrochel*, Study conducted by Biologic Safety Research, Inc. for Albion Laboratories, Inc., 1993.

- Coplin MS, Schuette S, Leichtmann G, Lashner B, *Tolerability of Iron: A Comparison of Bis-Glycino Iron II and Ferrous Sulfate*, Clinical Therapeutics, Vol. 13, No. 5, pg. 606 (1991).

- Olivares M, Pizarro F, Pineda O, Name JJ, Hertrampf E, Walter T, *Milk Inhibits and Ascorbic Acid Favors Ferrous Bis-Glycine Chelate Bioavailability in Humans*, Journal of Nutrition, Vol. 127, pg. 1 (July 1997).

- Allen LU, Bovell-Benjamin AC, Viteri F, *Iron is Well Absorbed from Ferrous Bisglycinate (Ferrochel) Added to a High Phytate, Whole Maize Meal*, Presented at Bioavailability 1997 Conference; Experimental Biology Conference; American Dietetic Association Conference; and International Union of Nutritional Sciences Conference.

- Ashmead HD, Gualandro SFM, Name JJ, *Increases in Hemoglobin and Ferritin Resulting from Consumption of Food Containing Ferrous Amino Acid Chelate (Ferrochel) versus Ferrous Sulfate*, Trace Elements in Man and Animals - 9 (TEMA - 9), Ottawa, Canada: NRC Research Press, pg. 284 (1997).

- Pineda O, Ashmead HD, Perez JM, Lemus CP, *Effectiveness of Iron Amino Acid Chelate on the Treatment of Iron Deficiency Anemia in Adolescents*, Journal of Applied Nutrition Vol. 46, No. 1&2, pg. 2 (1994).

- Queiroz S de S, Torres MA de A, *Anemia Carencial Ferropriva: Aspectos Fisiopatológicos e Experiência com a Utilização do Leite Fortificado com Ferro*, Pediatria Moderna, Vol. 31, Edição Especial (Julho1995).

- Fisberg M, Braga JAP, Kliamca PE, Ferreira AMA, Berezowski M, *Utilização de Queijo Petit Suisse na Prevenção da Anemia Carencial em Pré-escolares*, Clinica Pediátrica, Vol. 19, No. 6, pg. 14 (1995).

- Fox TE, Eagles J, Fairweather-Tait SJ, *Bioavailability of an Iron Glycine Chelate for Use as a Food Fortificant Compared with Ferrous Sulphate*, Trace Elements in Man and Animals - 9 (TEMA-9), Ottawa, Canada: NRC Research Press, pg. 460 (1997).

- Gualandro SFM, Name JJ, *Anemia and Iron Deficiency in a Population in Brazil. The Effect of the Consumption of Food Containing Ferrous Amino Acid Chelate or Ferrous Sulfate*, Presented at the 26th Congress of the International Society of Hematology, Singapore, August 27, 1996.

- Name JJ, *Food Fortification with Amino Acid Chelated Minerals*, International Conference on Human Nutrition, sponsored by Albion Laboratories Inc., Salt Lake City, Utah (January 21–22, 1995).

- Paiz R, Pineda O, *Deficiencia de Hierro y Anemia Ferropriva en al Infancia*, Ágora Médica, Vol. 2, No. 1, pg. 4 (1996).

Respectfully submitted pursuant to the provisions of the Regulation this 20th day of April, 1999.

The Company:

ALBION LABORATORIES INC.

James C. Hyde,
Vice President & General Counsel

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EXHIBIT A

(Attached to and made a part of the
Notice to U.S. FDA of "GRAS" Determination
for Ferrochel dated April 20, 1999)

WRITTEN EXPERT PANEL STATEMENT

EXPERT PANEL STATEMENT REGARDING GRAS STATUS OF FERROCHEL™, AN IRON AMINO ACID CHELATE

For purposes of making a self-determination of "generally recognized as safe" ("GRAS") according to applicable requirements of the U.S. Food and Drug Administration ("FDA") set forth at 21 C.F.R. §170.30 and 170.35, the undersigned individuals were asked by Albion Laboratories, Inc., a Utah corporation whose headquarters are located in Clearfield, Utah (the "Company"), to independently review information and data about its product, Ferrochel™, an iron amino acid chelate manufactured under the Company's patented processes (sometimes referred to as the "Product"). The Company intends the use of the Product to include food fortification and dietary supplementation. The undersigned, Joseph F. Borzelleca, Ph. D., W. Gary Flamm, Ph. D., and Allan L. Forbes, M.D. (collectively the "Panel"), are well-established food safety experts, qualified by training and many years of relevant national and international experience in evaluating the safety of food and food ingredients.

The Company provided extensive information on the safety, functionality and use of Ferrochel, which was independently reviewed by each of the Panel members. In addition, the Panel members relied on a search of scientific literature, other relevant information and their respective years of professional experience assessing related matters. A meeting to review the findings of the Panel was convened in Washington D.C. and included members of the Panel and technical and legal representatives of the Company.

Ferrochel is a highly stable chelate of ferrous iron and glycine. Chemically it is ferrous bisglycinate chelate, CAS No. 20150-34-9. It can be added to most foods without significant alteration of organoleptic properties. Studies have shown that iron as Ferrochel is highly bioavailable. These studies demonstrate that Ferrochel has ideal properties for food fortification. The Product is approved in several countries for use as a fortificant in a variety of foods. In addition, it has been employed internationally in several government intervention programs to redress iron deficiency anemia. Ferrochel is also marketed as a dietary supplement for human consumption in the United States, Canada, Europe, and Latin America.

Studies in rats show that Ferrochel has a low order of acute oral toxicity, the LD50 being 2800 mg/kg body weight. In a subchronic study conducted in accordance with FDA guidelines and applicable Good Laboratory Practices, Ferrochel was fed to Sprague Dawley rats for 90 days at doses of 100, 250 and 500 mg/kg bw/day. There were no dose-dependent, treatment-related, statistically significant differences between control and treated animals with respect to mortality, appearance, behavior, physical findings, body weight and body weight gain, food consumption (and efficiency), clinical chemistry and hematology parameters, absolute and relative organ weights, and macroscopic and microscopic findings. Hepatic non-heme iron concentrations were elevated indicating Ferrochel was absorbed. The No Observed Adverse Effect Level ("NOAEL") for Ferrochel was determined to be greater than 500 mg/kg bw/day (the highest dose) under the conditions of this study. While toxicity was not achieved at the highest dose of this study, the Panel considers the toxicity of iron sufficiently well understood to obviate the need to observe overt signs of iron toxicity.

Tolerance studies comparing Ferrochel to ferrous sulfate, designed as double-blind crossover trials, have shown that premenopausal women taking 50 mg elemental iron daily in capsule form as ferrous sulfate or Ferrochel experienced fewer moderate-to-severe side effects with Ferrochel (21% compared to 37%, $p<0.05$).

A number of well conducted studies have demonstrated Ferrochel's bioavailability in animals and humans. For example, clinical studies in young children have demonstrated the effectiveness of milk fortified with 3 mg of Ferrochel iron per liter in repleting hemoglobin in iron deficiency anemia. A series of other published clinical studies confirm Ferrochel's effectiveness as a dietary supplement or food fortificant

At the outset of the Panel's review of the referenced studies, it was reasonable to consider the possibility that a form of iron overload could occur in humans consuming significant amounts of the iron amino acid chelate for two related reasons: (i) the Product's high bioavailability, and (ii) the hypothesis that, because of its high bioavailability, the absorption of iron as Ferrochel might be regulated by a mechanism different from the usual method of iron absorption regulation, which is largely dependent on body iron stores and the iron nutriture of the individual. The numerous clinical studies using Ferrochel confirm that absorption of iron derived from Ferrochel is regulated in the usual manner as for other iron compounds. Hence, there is no risk of iron overload in the absence of infrequent genetically determined abnormality of iron absorption and metabolism, which require individualized diagnostic procedures and therapeutic regimens. This same absence of iron overload applies to all sources of dietary iron. Therefore, in terms of regulation, Ferrochel is not unique.

In the United States over 50 years of experience have been accumulated with respect to iron usage, both as a supplement and a fortifier for basic staples and other conventional foods such as flour and various forms of other cereal based products, including breakfast cereals. This history of use has been remarkably problem free. The only clinically significant problem has been accidental acute iron poisoning characterized by acute gastrointestinal bleeding and other complications which can have fatal outcomes. This usually occurs in toddlers who gain access to a bottle of the parents' iron supplements and quickly ingest huge amounts of iron. This problem has been substantially reduced by the U.S. Consumer Products Safety Commission which by regulation requires that iron supplement containers must have child resistant safety closures (except for extremely low potency products).

Since the beginning of World War II there has been clear guidance on the amount of individual essential nutrients required to sustain normal health in the form of Recommended Dietary Allowances ("RDA") established by the Food and Nutrition Board of the National Academy of Sciences ("FNB/NAS"). The RDAs have been revised at approximately five year intervals. Currently, the RDAs for iron range from 10 mg/day for infants to 18 mg/day for adolescent and pre-menopausal women, with a further recommendation of 30 to 60 mg/day as supplemental iron during pregnancy. A related publication from members of the FNB/NAS provides a range from 6.6 mg/day for 3 to 6 month old infants to 45 mg/day during all three trimesters of pregnancy (including 30 mg/day of supplemental iron). The RDAs have recently been translated into

Recommended Daily Intakes ("RDI") by FDA for labeling purposes, but the levels remain essentially the same as the RDAs.

A second guideline is the FDA's Current Good Manufacturing Practices ("CGMP") (generally found at 21 CFR §§182 and 110) which clearly state that ingredients added to foods (or supplements) should not exceed the amounts reasonably required to achieve an intended purpose. These regulations in one form or another have been in place for many years.

Both sets of guidelines (RDAs and CGMPs) have provided excellent guidance to manufacturers and distributors of iron fortified foods and iron supplements over many years. Hence, in view of the well established guidelines (historical, RDAs and CGMPs) designed for the protection of public health and the exceptionally high NOAEL of Ferrochel (>500 mg/kg bw/day), there is no need in the Panel's view to establish an arbitrary upper limit of use of Ferrochel as a dietary supplement or a food fortificant.

For purposes of food fortification, the Panel concludes that Ferrochel, meeting appropriate food grade specifications, is GRAS by scientific procedures limited only by applicable laws and regulations, including those Current Good Manufacturing Practices set forth at 21 C.F.R. §182.1(b), requiring, *inter alia*, that the quantity of the Product added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritional or other technical effect in food.

For purposes of dietary supplementation, the Panel concludes that Ferrochel, meeting appropriate food grade specifications, is GRAS by scientific procedures limited only by applicable laws and regulations including Current Good Manufacturing Practices.

DATED effective as of September 15, 1997.

JOSEPH F. BORZELLECA, Ph.D.

W. GARY FLAMM, Ph.D.

ALLAN L. FORBES, M.D.

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End Submission

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